REMARKS/ARGUMENTS

In response to the Office Action of January 5, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The title of the invention has been amended to correct a punctuation error in the reciting of Alzheimer's disease

(Alzheimers corrected to Alzheimer's).

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers, clearly indicate that Figures 2-5, 7, 9 and 10 show the mass spectrum profiles of the disclosed biopolymer markers, and to correct a punctuation error in the reciting of Alzheimer's disease (Alzheimers corrected to recite Alzheimer's).

Several protocols at pages 41-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (line 20), page 42 (line 11) page 43 (lines 2 and 16) and page 44 (line 6) were underlined in the original disclosure and do not indicate text amended herein.

The paragraph at pages 46-47 was amended to correct a punctuation error in the reciting of Alzheimer's disease (Alzheimers corrected to recite Alzheimer's). This paragraph was also amended to add the term "daltons" after the molecular weight of SEQ ID NOS: 1 and 2 and to delete the term "having" for consistency of language.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 50, line 10 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:3). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, line 17 to page 47, line 12 and Figures 1 and 4.

Claim 44 has been amended to correspond with the biopolymer

marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 48, line 8 to page 49, line 17. Claim 44 was also amended to correct a grammatical error(an replaced and).

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Restriction

The Examiner has determined that the requirement for restriction (mailed on October 6, 2004) is still proper and therefore has made the requirement final.

Applicants have claimed the biopolymer markers (SEQ ID NOS:1-7)in a Markush-type grouping indicating that SEQ ID NOS:1-7 are alternatively usable (MPEP 803.02). In contrast to Applicants' presentation of SEQ ID NOS:1-7 in a Markush-type grouping, the Sequence Election Requirement presents each of SEQ ID NOS:1-7 as unrelated, patentably distinct sequences, thus introducing a contradiction into the prosecution history. Such contradictions can potentially diminish the value of any patent that may issue from the instant application. For example, since Applicants are required to elect a Group (and a single sequence) for prosecution on the merits, one reading the prosecution history may incorrectly assume

that Applicants admit that the biopolymer markers of SEQ ID NOS:1-7 are separate and distinct inventions.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:3 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:3 is found to be novel, methods and kits limited to its use should also be found novel.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by

the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner indicates that the Information Disclosure Statements filed on April 10, 1992, May 1, 2003 and September 29, 2003 have been considered as to the merits prior to the first action.

It is noted that the actual date of the first Information Disclosure Statement is April 10, 2002 and not April 10, 1992. Applicants assume that year 1992 is an inadvertent typographical error.

The references cited within the specification but not included in the above-mentioned Information Disclosure Statements provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Objections to the Specification

The Examiner notes the use of trademarks in the application (i.e. SEPHAROSE at page 41, lines 12 and 13 and TRITON at page 42, lines 8 and 22) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further

notes that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification at pages 41-45 to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed all of the Examiner's objections and respectfully request that the objections to the specification be withdrawn.

Rejection under 35 USC 112, second paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that claim 1 is vague and indefinite because the biopolymer is "diagnostic" for Alzheimer's disease.

"Diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease. It is not clear how the biopolymer marker will analyze the cause or nature of Alzheimer's disease. Applicants' intended meaning of "diagnostic" is not defined by the claims or the specification. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner suggests that the claim merely recite "detection of" Alzheimer's disease in order to obviate this rejection.

Applicants respectfully disagree with the Examiner's assertions.

The term "diagnostic" refers to the identification of a property or characteristic, usually regarding the health of an individual, such as, identifying a disease linked with the property or characteristic. It is clear from the multiple disclosures in the instant specification that the term "diagnostic" or "diagnose" refers to the identification of a disease; see, for example, page 5, lines 12-20; page 31, lines 19-22; page 32, lines 7-10; page 36, lines 9-12; page 49, line 18 to page 50, line 3; page 53, lines 4-7 and page 53, line 18 to page 54, line 6. According to the web site dictionary. com; the term "diagnostic" relates to or refers to use in diagnosis; use in serving to identify a particular disease or to a symptom or a distinguishing feature; and/or use in serving as

supporting evidence in a diagnosis (see attached definition as accessed from the internet; reference 1).

Neither the art nor the specification suggests that "diagnostic" refers to anything other than identification of a disease. Thus, Applicants respectfully submit that the Examiner has no basis for asserting that the term "diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease.

However, in the interest of compact, efficient prosecution, Applicants have amended the claim to remove the term "diagnostic".

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 USC 112, second paragraph be withdrawn.

Rejection under 35 USC 101

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 101 because the claimed invention allegedly is not supported by a either a specific, substantial, credible or asserted utility or a well-established utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

The Examiner asserts that applicants have disclosed in the

specification that SEQ ID NO:3 is measurable in patients with Alzheimer's disease but is undetectable or regulated differently in normal patients (see pages 46 and 47).

Applicants respectfully assert that this statement made by the Examiner is incorrect.

Pages 46 and 47 of the instant specification indicate that practice of the disclosed procedures identifies the peptide of SEQ ID NO:3 as related to Alzheimer's disease. Contrary to the Examiner's assertion no assumptions about the presence and/or regulation of the peptide (SEQ ID NO:3) are found at pages 46 and 47 of the instant specification. Furthermore, again contrary the Examiner's assertion, Figure 1 of the instant specification discloses that the claimed peptide is detectable in age matched control patients but is not detectable in Alzheimer's patients.

Additionally, the Examiner asserts that the disclosure appears to require not only SEQ ID NO:3 but a combination of SEQ ID NOS:1-7 for the identification of Alzheimer's disease (see page 47).

Applicants respectfully assert that this statement made by the Examiner is also incorrect.

No where does the specification indicate that a combination of markers (SEQ ID NOS:1-7) is a requirement for the identification of Alzheimer's disease through use of the disclosed methods.

At page 9 of the Office Action mailed on January 5, 2005, the Examiner asserts that SEQ ID NO:3 does not appear to be a marker

for Alzheimer's disease (clearly distinguishing the disease from normal or control patients).

Applicants respectfully disagree with the Examiner's line of reasoning and assert that SEQ ID NO:3 is useful for diagnosis and treatment of Alzheimer's disease since it was found to evidence a link to Alzheimer's disease (an "asserted" utility).

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed peptide (SEQ ID NO:3).

Furthermore, Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13; page 35, lines 14-18; page 46, line 17 to page 47, line 12; and Figures 1 and 4).

The claimed peptide (SEQ ID NO:3) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, Alzheimer's disease, thus the invention has a specific utility.

Additionally, if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as

established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The risk for developing Alzheimer's disease increases with age. Thus, advances in the diagnosis and treatment of Alzheimer's disease would greatly benefit the elderly population . The claimed peptide (SEQ ID NO:3) represents an advance in Alzheimer's research; a "real-world" use to benefit the public (i.e. the elderly population), which satisfies the precedent set in *Nelson*. Thus, the claimed peptide (SEQ ID NO:3) additionally has a substantial utility.

It has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

Although the Examiner should regard Applicants' statement of asserted utility sufficient to satisfy the requirements of 35 USC 101, the Examiner lists several reasons which allegedly support her argument that the claimed invention has no utility.

First, the Examiner asserts that the figures do not identify SEQ ID NO:3 (which band corresponds to SEQ ID NO:3) thus a correlation to Alzheimer's disease is impossible.

Applicants respectfully assert that the Examiner's statement is incorrect.

SEQ ID NO:3 is identified by a molecular weight of about 1498

daltons at page 46, line 22 to page 47, line 1 of the originally filed specification. Figure 4 shows the characteristic profile obtained by mass spectrometry of an ion of about 1498 daltons. The title of the spectrum shown in Figure 4 indicates that the peptide was identified from the HiS 1 Scrub gel C6. Figure 1 shows the photograph of the His 1 Scrub gel in which Band #6 is labeled. All of the figures are part of the specification as originally filed. Thus, contrary to the Examiner's assertion, the figures do identify the band from which SEQ ID NO:3 was obtained.

The Examiner asserts that no clear difference in up and down regulation of the marker can be determined; the correlation with respect to Alzheimer's disease is not evident and thus SEQ ID NO:3 does not appear to be a marker for Alzheimer's disease (clearly distinguishing the disease from control or normal patients).

Applicants respectfully disagree with the Examiner's assertions.

The gel in Figure 1 show an increased expression of Band #6, from which SEQ ID NO:3 was obtained and identified, in the samples obtained from age-matched control patients as compared with the samples obtained from Alzheimer's patients. Thus, contrary to the Examiner's assertion, a clear difference in up and down regulation of the marker can be determined from the data presented in the instant specification.

In the medical arts proteins found to be differentially

expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics. For example, when a peptide is identified in a body fluid sample from an Alzheimer's patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 2) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker. Thus, when one of skill in the art observes the claimed peptide differentially expressed between Alzheimer's disease patients and age matched control patients; one of skill in the art would connect the peptide with potential diagnostics and/or therapeutics for Alzheimer's disease and would immediately appreciate why applicants regard the claimed peptide (SEQ ID NO:3) as useful, indicating that the utility of the claimed peptide (SEQ ID NO:3) is well-established. Thus, contrary to the Examiner's assertion a correlation between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease is evident.

It has been known for over a decade that apolipoprotein E is involved with the pathogenesis of Alzheimer's disease (see attached

abstracts of Blennow et al. Neuroreport.5(18):2534-2536 1994; reference 3 and Wisniewski et al. Biochem Biophy Res Communication 192(2):359-365 1993; reference 4).

Wisniewski et al. discloses that apolipoprotein E binds to beta-amyloid (β-amyloid) in senile plaques (a hallmark of Alzheimer's disease).

Upon analysis of the presence of apolipoprotein E in cerebrospinal fluid Blennow et al. found a significant reduction of apolipoprotein E in Alzheimer's disease when compared to controls. This finding was sufficient for Blennow et al. to suggest that apolipoprotein E was involved in the pathogenesis of Alzheimer's disease.

At page 46, lines 22-23 of the instant specification as originally filed, the claimed peptide (SEQ ID NO:3) is identified as a fragment of apolipoprotein E. The data presented in Figure 1 indicates that apolipoprotein E is not detectable in samples obtained from Alzheimer's disease patients. The instant inventors hypothesized that apolipoprotein E binding to β-amyloid in the brain resulted in the reduction of apolipoprotein E in samples obtained from Alzheimer's patients. One of skill in the art, considering the known involvement of apolipoprotein E with β-amyloid in the brain of Alzheimer's patients, would find such a hypothesis to be reasonable.

Therefore, one of ordinary skill in the art would recognize

the linkage between apolipoprotein E and Alzheimer's disease and thus would also find the suggestion of SEQ ID NO:3 as marker for Alzheimer's disease entirely reasonable.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner makes the following assertions:

Claim 1 is directed to a biopolymer consisting of SEQ ID NO:3 indicative of Alzheimer's disease. The Examiner contends that the specification does not support this assertion. The specification (in particular page 46) and the figures do not definitively correlate the claimed marker consisting of SEQ ID NO:3 to Alzheimer's disease. The specification recites that the biopolymer consisting of SEQ ID NO:3 was found or regulated differently in the serum of patients suffering from Alzheimer's disease on page 46,

but the specification does not contain any data supporting this contention and the figures do not identify SEQ ID NO:3 as a definitive marker for Alzheimer's disease. Therefore, it is unclear how SEQ ID NO:3 was identified as "notable" or how it was deemed "evidentiary" of a disease state. There is nothing in the disclosure that would enable one to choose SEQ ID NO:3 as a notable sequence among an infinite number of possible proteins or peptides present in a patient sample.

Applicants respectfully disagree with all of the Examiner's assertions.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:3 is diagnostic for Alzheimer's disease, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:3 is linked to Alzheimer's disease.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 5). The instant specification fully supports a connection and/or an association of the claimed peptide with Alzheimer's disease. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a

plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:3) is linked and/or associated with Alzheimer's disease.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:3, a peptide which the instant specification identifies as related to Alzheimer's disease. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for Alzheimer's disease, nor does it recite that the claimed isolated peptide is related to Alzheimer's disease, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and

excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

At page 46, line 22 to page 47, line 1 of the specification as originally filed, SEQ ID NO:3 is identified as having a molecular weight of about 1498 daltons. The description of Figure 4 at page 37 indicates that the spectra depicted in the figure is that of ion 1498 (SEQ ID NO:3). The spectra shown in Figure 4 was obtained from Band #6(resolved from a sample obtained from a patient age matched with an Alzheimer's disease patient) as shown in the gel of Figure 1. The descriptions of the figures have been amended to clarify that the data shown in the figures is representative of the claimed and/or disclosed peptides.

Figure 1 demonstrates that the biopolymer marker peptide (Band #6; SEQ ID NO:3) is present in body fluid samples obtained from patients age matched with Alzheimer's disease patients, but is not present in body fluid samples obtained from Alzheimer's patients. Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to Alzheimer's disease.

The specification, as originally filed, does provide a precise protocol on how to analyze the data obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the

data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 47, lines 20-22 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics. For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics

2:59-65 2000; reference 6). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, line 21 to page 39, line 2 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on

differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (SEQ ID NO:3), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 1 is a photograph of a gel showing the results of HiS resin (scrub) column chromatography as carried out with a set of 9 samples; 4 serum samples from Alzheimer's disease patients (lanes

1-4, as read from the left), 4 serum samples from patients age matched with the Alzheimer's patients (lanes 5-8, as read from the left) and 1 sample of normal serum (pooled from different "normal" patients; lane 9, as read from the left). Patient serum samples AG-AD-H-S-004 and AG-AD-H-S-005, shown in lanes 7 and 8, respectively, display a band, numbered Band #6, from which the claimed peptide was isolated. These patients are all patients who were age matched to the Alzheimer's patients participating in the experiment. Band #6 is not evident in any of the Alzheimer's disease samples (lanes 1-4) or in the normal serum sample, lane 9.

The data presented in the figures, derived from the working examples, discloses that the claimed peptide (SEQ ID NO:3) is differentially expressed between Alzheimer's disease and a "normal" physiological state of patients age matched to the Alzheimer's patients, thus it can be reasonably predicted that such peptide is linked to Alzheimer's disease. Furthermore, the figures identify SEQ ID NO:3 and the specification discloses how such a sequence was identified as a notable sequence in relation to Alzheimer's disease.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:3) and Alzheimer's disease.

Considering the above comments, it is clear that both the

specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The Examiner asserts that there is no correlation between the procedure for screening samples from patients suspected of having a variety of different diseases, the presence/absence of SEQ ID NO:3; and the determination, prediction, assessment of at least one particular disease state like Alzheimer's disease. There is no disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said marker. The disclosure is lacking any teaching for how the identified sequence will be utilized to identify therapeutic avenues and regulation of a disease state. There is no disclosure designating how the sequence could be utilized therein, enabling one of ordinary skill in the art to use the sequence in the diagnostic method.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether

everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite any disease state other than Alzheimer's disease, nor do the pending claims recite identification of therapeutic avenues or methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that any of the sequences (in particular SEQ ID NO:3) are unique molecular markers for Alzheimer's disease or any other disease and the prior art teaches that disease markers are highly unpredictable and require extensive experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that SEQ ID NO:3 is linked to Alzheimer's disease, however, do not claim that SEQ ID NO:3 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed SEQ ID NO:3 is related to Alzheimer's disease, it does recognize that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 2) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker for Alzheimer's disease. When one of skill in the art observes differential expression of the claimed peptide between Alzheimer's disease patients and non-diseased patients; one of skill in the art would connect this peptide with potential diagnostic and/or therapeutics for Alzheimer's disease.

Thus, Applicants respectfully submit that since the

specification demonstrates a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of Alzheimer's disease, the requirement of "how to use" under 35 USC 122, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease to be reasonable.

It has been known for over a decade that apolipoprotein E is involved with the pathogenesis of Alzheimer's disease (see attached abstracts of Blennow et al. Neuroreport.5(18):2534-2536 1994; reference 3 and Wisniewski et al. Biochem Biophy Res Communication 192(2):359-365 1993; reference 4).

Wisniewski et al. discloses that apolipoprotein E binds to beta-amyloid (β-amyloid)in senile plaques (a hallmark of Alzheimer's disease).

Upon analysis of the presence of apolipoprotein E in cerebrospinal fluid Blennow et al. found a significant reduction of apolipoprotein E in Alzheimer's disease when compared to controls. This finding was sufficient for Blennow et al. to suggest that apolipoprotein E was involved in the pathogenesis of Alzheimer's disease.

At pages 46-47 of the instant specification as originally

filed, the claimed peptide (SEQ ID NO:3) is identified as a fragment of apolipoprotein E. The data presented in Figure 1 indicates that apolipoprotein E is not detectable in samples obtained from Alzheimer's disease patients. The instant inventors hypothesized that apolipoprotein E binding to β-amyloid in the brain resulted in the reduction of apolipoprotein E in samples obtained from Alzheimer's patients. One of skill in the art, considering the known involvement of apolipoprotein E with β-amyloid in the brain of Alzheimer's patients, would find such a hypothesis to be reasonable.

Therefore, one of ordinary skill in the art would recognize the linkage between apolipoprotein E and Alzheimer's disease and thus would also find the suggestion of SEQ ID NO:3 as marker for Alzheimer's disease entirely reasonable.

The Examiner asserts that the disclosure has not addressed issues taught in the prior art as crucial to the discovery of a biopolymer marker.

The Examiner cites an article Hampel *et al* (Journal of Neural Transmission 111:247-272 2004) which is allegedly relevant to the instant invention. According to the Examiner, Hampel *et al* reports on the difficulty involved in the discovery of marker candidates for Alzheimer's. The Examiner states that several required criteria must be met when determining a marker for Alzheimer's, including; indication of disease progression, heterogeneity of the clinical

population, feasibility of testing, assay sensitivity, frequency of assessments, stability, standardization, dynamic range and comparative analysis. The Examiner seems to believe that since the specification allegedly lacks any of the criteria stated in the Hampel *et al* reference, it would require undue experimentation for one skilled in the art to make and use the invention.

Applicants respectfully assert that the criteria suggested by Hampel *et al* do not control the issue of enablement with regard to the instant invention. The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112 is satisfied. Applicants claim that the presence of a biopolymer marker peptide (SEQ ID NO:3)is linked to Alzheimer's disease; a statement which is enabled by the data presented in Figures 1 and 4. The claimed method involves a simple observation of the presence of the marker (as shown in Figure 1) in a gel, and conducting mass spectrometry analysis to identify the markers present in the gel. Hampel et al. disclose a study similar to that of the instant inventors; see page 260, last paragraph. In this study the content of body fluid obtained from MCI (mild cognitive impairment) patients was compared with the content of body fluid obtained from normal control patients. The MCI patients showed an elevated level of a protein, p-tau_{231}, in comparison to the healthy control patients. Hampel et al. deemed the results of this study adequate

to suggest that high levels of p-tau_{231} may be a predictor for progressive cognitive decline in subjects with MCI. This disclosure of Hampel et al. demonstrates further that when elevated levels of proteins are found associated with a disease state, the protein is considered useful for potential diagnostics and/or therapeutics in the disease condition. Thus, in contrast to the Examiner's assertion, the article of Hampel et al. lends support to the argument that the instant invention is enabled. Based upon the above-discussion, Applicants respectfully submit that compliance with the "required" criteria for a diagnostic assay according to Hampel *et al* is not necessary to show that the instant invention is enabled. When subjected to the "test for enablement" the Examiner's argument is not sufficient to support the enablement rejection; since the association of the claimed biopolymer marker (SEQ ID NO:3)with Alzheimer's disease carries with it a connotation of use for diagnostics.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful

application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for Alzheimer's disease.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect

oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:3) and Alzheimer's disease.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for

clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05).

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

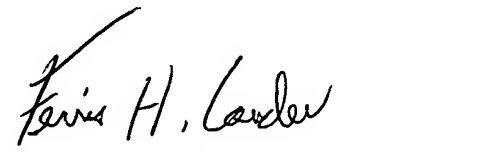
In conclusion, Applicants claim that the differential expression of SEQ ID NO:3 between Alzheimer's patients and patients age matched with the Alzheimer's patients evidences a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease and would further recognize how to use the claimed peptide (SEQ ID NO:3) as a marker for

Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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